Multiple sclerosis in an adrenoleukodystrophy carrier

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Abstract

X-linked adrenoleukodystrophy (X-ALD) is a rare inherited metabolic disorder, in which accumulation of very long chain fatty acids (VLCFAs) results in damage to the central nervous system. As the disease is X-linked, males are affected severely, but female carriers may also present with neurological symptoms. We report the case of a young adult female, who presented with episodic sensorimotor symptoms. Although she was a heterozygous female carrier of X-ALD, subsequent investigations confirmed a diagnosis of multiple sclerosis (MS). To the best of our knowledge, this is the first reported case of a female X-ALD carrier in which the clinical features were more consistent with co-existent MS than ALD-related pathology. The case serves as a reminder that alternative, more common diagnoses should also be considered in carriers of rare neurological syndromes.

Case Report

A 29-year-old female was referred to the Adult Inherited Metabolic Disease clinic with a four-year history of episodic sensorimotor symptoms. The first episode began with numbness in the right foot, spreading to affect the right leg, trunk, arm and face, lasting six weeks before spontaneously resolving completely. Subsequently, a further eight episodes of similar neurological disturbance occurred, each affecting her right side, lasting between twelve days and six weeks, and followed by recovery. The last attack was characterized by weakness and incoordination of the right leg, associated with dizziness and difficulty walking, lasting twelve days. She also reported mild urinary urgency and frequency. There were no other neurological symptoms. At initial assessment, she complained of residual numbness affecting her entire right hand, and struggled with prolonged writing. There was no other medical history. She is an ex-smoker and drinks moderate alcohol.

Her only son was diagnosed with childhood cerebral ALD (CC-ALD) and died at the age of six years, despite bone marrow transplantation. She has no daughters. Her mother and sole sibling, a sister, are known X-linked adrenoleukodystrophy (X-ALD) carriers, but her maternal grandmother does not have the mutation. The maternal grandfather died of a probable myocardial infarction in his late 60s and was not genotyped; he did not have any gait disturbance. Her ten-year-old nephew underwent bone marrow transplantation and is in remission. Another nephew has magnetic resonance imaging (MRI) changes consistent with ALD, and was asymptomatic at age three years.

At the time of presentation to the Neurology service, general physical examination was unremarkable. Visual acuity was 6/6 and colour vision 13/13 bilaterally, fundi were normal, and she had a full range of eye movements. There was mild pyramidal weakness of the right leg. Deep tendon reflexes were bilaterally brisk, but both plantars were flexor. Coordination and sensation were normal. The Extended Disability Status Score (EDSS) was 2.0.

Baseline haematological, biochemical and immunological blood tests were normal. There was no evidence of adrenal dysfunction, with normal serum cortisol and adrenocorticotrophic hormone (ACTH) levels. Plasma very-long-chain fatty acids (VLCFA, Sheffield Children's Hospital) were elevated, C26:0 2.51 μmol/L (reference range 0.33-1.50), C24:0 60 μmol/L (14-80), C26/C22 0.045(0.005-0.030), C24/22 1.07(0.44-0.97). Gene testing for the ABCD1 mutation was positive.

Cranial MRI demonstrated several areas of increased signal in a periventricular distribution, consistent with demyelination (Figure 1).

Cerebrospinal fluid (CSF) analysis was normal (glucose 3.1 mmol/L, protein 302 mg/L, white cell count 2×10^6/L) apart from evidence of oligoclonal band synthesis in CSF (serum normal, type 2 pattern). Visual evoked potentials (VEPs) were normal.

Based on the relapsing-remitting history, the examination findings, the MRI appearances and the unmatched CSF oligoclonal bands, a diagnosis of relapsing-remitting multiple sclerosis (MS) was made. As there had been three clinical episodes within the previous two years, treatment with subcutaneous interferon β-1a (Rebif 44 mg) was started. Subsequently, this was changed to intramuscular interferon β-1a (Avonex), because of injection site reactions.

Initially, the frequency and severity of her relapses reduced over the ensuing three years, with two episodes of mild sensory symptoms at 6 months (paraesthesia affecting the right leg, lasting for a week) and 24 months (sensory symptoms affecting her left side). However, she then suffered two further attacks over the next 12 months, resulting in residual weakness in both legs and paraesthesia to the waist. Her EDSS score increased to 4.0. Repeat cranial MRI showed new lesions and contrast enhancement. β-interferon was stopped and therapy with natalizumab initiated in February 2009. There have been no further episodes of neurological symptoms to date, other than a mild episode of pins and needles in both feet, associated with difficulty climbing stairs in January 2010, which improved spontaneously. Her current EDSS is 3.5.

Discussion

X-linked adrenoleukodystrophy (X-ALD) is a clinically heterogeneous disorder with an overall incidence of 1:16,800. The disease is caused by mutations in the ABCD1 gene on the X chromosome at q28, resulting in dysfunction of the peroxisomal membrane transporter protein, a member of the ATP-binding cassette transporter superfamily. The function of this protein is unclear; it may be involved in the transfer of VLCFA across the cell membrane. In X-ALD, VLCFA accumulate in the adrenal glands, testes and nervous system. Demyelination ensues in the brain, spinal cord, and peripheral nerve. The clinical result is progressive organ dysfunction, predominantly affecting the adrenal glands and the white matter of the central nervous system.[1-4]

Several phenotypic variants of X-ALD exist. The cerebral variants differ in age of onset. Childhood-onset cerebral ALD (CC-ALD) is the most severe form, and manifests as early neurological dysfunction (including pseudobulbar palsy, dementia, personality change, cortical blindness, deafness, and ataxia) and adrenal

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insufficiency. Most patients die within two to three years of disease onset. Adolescent-onset cerebral ALD is much less common and usually occurs between the ages of 10 to 21. Adult-onset cerebral ALD resembles the childhood cerebral form, but psychiatric manifestations are more prevalent.[1-3]

In the adrenomyeloneuropathy variant (AMN), patients usually present later, in the second to fourth decades, with spinal cord dysfunction, frequently spastic paraparesis. The presentation may resemble primary progressive MS or hereditary spastic paraparesis. Life expectancy is normal. Approximately 50% of these patients have changes on cranial MRI, which may resemble the neuroradiological appearances of MS.[2]

Female carriers, heterozygous for the X-ALD mutation, are usually asymptomatic, but may present with mild cerebral or adrenal involvement, which progresses very slowly. The mean age of onset is 40 years and the clinical features may resemble the syndrome seen in males with AMN.[3]

The pathology of cerebral X-ALD and AMN is thought to be distinct. In cerebral X-ALD, inflammatory demyelinating lesions are seen, which mainly affect the parieto- occipital white matter. Involvement of corpus callosum is reported.[5] Lesions are characterized histologically by the presence of lymphocytes, macrophages and reactive astrocytes.[3] In pure AMN, distal axonopathy is seen, with loss of axons and myelin also commonly affecting the gracile and corticospinal tracts.

The typical cranial MRI appearances differ according to the clinical phenotype. Extensive confluent symmetrical changes may be seen in cerebral variants. In AMN, the MRI may be normal. Fatemi and colleagues investigated the MRI changes in heterozygous female carriers of X-ALD and found that only 4% had changes in the brain attributable to the disease, with bilateral symmetrical white matter abnormalities.[6] Eighty-six percent had normal scans, and the remainder showed changes consistent with age, cerebrovascular disease or previous trauma. In another study, Kumar and colleagues reported a prevalence of 20% brain MRI abnormalities in female X-ALD heterozygotes, most commonly a mild increase in signal intensity in the parieto-occipital or frontal white matter.[7]

An oligoclonal banding pattern in the CSF is found in the majority of patients with MS and provides strong support for the diagnosis in the appropriate clinical context. However, oligoclonal bands may also be seen in ALD (Dr. Geoffrey Keir, personal written communication, 14/10/08) but the prevalence remains unclear.

The treatment of MS and ALD is very different. In ALD, dietary measures have been proposed as a potential treatment strategy. These have included restriction of dietary saturated fats rich in VLCFA, and a supplemented intake of monounsaturated fats, such as Lorenzo's oil, but the results so far have been disappointing.[8] Bone marrow transplantation is an effective therapy for childhood cerebral ALD when performed promptly after onset of symptoms but is much less successful in adolescent or adult cerebral ALD. An inflammatory response in the brain has been hypothesized to underlie the observed widespread white matter changes, especially in the cerebral forms of adrenoleukodystrophy, but a number of therapeutic trials with immunosuppressive drugs, such as cyclophosphamide, cyclosporin and β-interferon have not resulted in any significant clinical benefits.[3]

There are published case reports of female heterozygous X-ALD carriers presenting with neurological symptoms suggestive of MS, in whom a diagnosis of ALD was subsequently established, based on clinical and biochemical findings.[9-11] Stockler and co-workers reported a young woman who presented with transient visual symptoms.[9] Visual evoked responses were delayed in the right eye, and cranial MRI revealed two partially confluent periventricular lesions. The CSF was not examined in this patient. The authors concluded that the neurological syndrome was more likely ALD-related than MS. Krenn et al reported a 40 year old female with spastic paraparesis, sensory and bladder symptoms and visual disturbance.[10] Cranial MRI showed periventricular lesions, intrathecal immunoglobulin was present and VEPs were pathological. The authors concluded that the symptoms were related to ALD.

In our patient, the diagnosis of MS was established on the basis of the relapsing-remitting history, typical MRI changes (including contrast enhancement, which does not appear to have been reported previously in ALD), positive oligoclonal bands in CSF, and favourable response to disease-modifying therapy. In particular, the predominance of sensory symptoms with complete resolution was considered more consistent with MS than ALD. To the best of our knowledge, this is the first reported case of MS in an ALD carrier, and serves as a reminder that neurological symptoms in carriers of rare diseases are not always related; sometimes more common coexisting conditions explain the presentation.

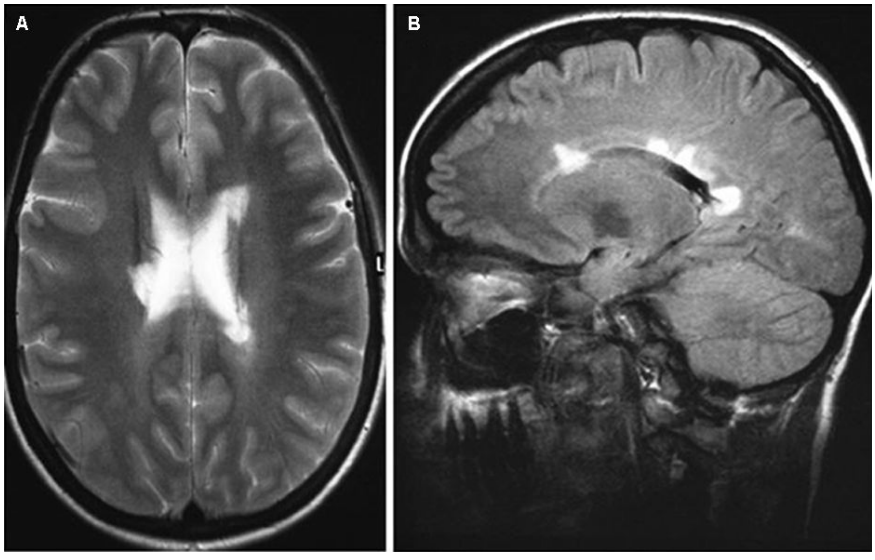

Figure 1. (A) Axial T2-weighted and (B) sagittal fluid-attenuated inversion recovery magnetic resonance imaging sequences show periventricular hyperintense lesions in a typical pattern for multiple sclerosis.

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